REMARKS

The withdrawal of the rejection of claims 1, 11, 18-19, 33, 43, and 50-51 under 35 U.S.C. § 112, second paragraph, has been noted.

Claims 5-7, 13, and 61 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Reconsideration is requested in view of this Amendment.

Claim 1 has been amended to add a phrase "is prepared by using dual retard technique to control the release of the high dose high solubility activity active ingredient, wherein the said dual retard technique is a combination of a matrix formulation and a reservoir formulation". The basis for this amendment is found in the specification at page 4, para 0056 . Claims 20 and 23 have been amended to point out that the dosage form consist of the recited active ingredients.

Claims 5, 7 and 61 have been amended to point out the Eudragit polymers by their chemical names. Claim 13 has been canceled and is no longer at issue. For these reason, it is requested that this ground of rejection be withdrawn.

Claims 1, 5-7, 11-15, 18-20, 23, 26-27, 30-32, 52, 55, 57-58, and 60-75 were rejected under 35 U.S.C. §103(a) as being unpatentable over Timmins et al.(Timmins) in view of Boswell.

Reconsideration is requested.

The problem addressed by the present invention is the art recognized difficulty in formulating matrix controlled release

formulations of highly soluble drugs which is difficult because highly soluble drugs often have a tendency to exhibit a release profile that often results in dose dumping or a burst release that makes the matrix formulation unacceptable for use with a highly soluble drug. This problem is exacerbated by the fact that many modified release dosage forms contain comparatively large amounts of a highly soluble active ingredient and it is often necessary to include large amounts of suitable excipients to achieve appropriate controlled release profiles. The resulting over sized dosage form is difficult to swallow. This description of the state of the art is acknowledged by Timmins (col.4, lines 58-61). Hence a technique is needed, which can effectively control the release of the highly soluble active ingredient without requiring an over sized dosage form.

Timmins discloses a biphasic controlled release delivery system for highly soluble drugs such as metformin hydrochloride, which operates by the use of ingredients that operate to cause the formulation to have a prolonged gastric residence time. The prolonged gastric residence time is achieved by the use of materials that swell following contact with gastric fluids to the extent that the swollen dosage form cannot pass the pyloric sphincter. Timmins does not disclose a dosage formulation having an immediate release-inner portion where a top surface of the immediate release inner portion remains uncovered. This feature is clearly pointed out in claims 1 and 75 of the present application.

To utilize the Timmins technique of formulation, it is necessary to provide a very bulky formulation for higher doses of a drug such as metformin hydrochloride..For instance, the cited example provides a formulation of 500mg metformin with a tablet weight of 1.0gm.

It is apparent from the Timmins specification that the Timmins dosage formulation operates by increasing the time that the dosage

remains in the stomach because the dosage formulation is designed to swell in the stomach so that the dosage formulation will have a prolonged residence time. This essential functional characteristic can only be achieved by the use of polymers that swell on contact with water. (Cf. Timmins col.20, lines 55-60). Therefore, although Timmins has disclosed a dosage formulation having an inner solid particulate phase and an outer solid continuous phase in which the inner solid particulate phase is embedded and dispersed throughout, that dosage form uses one or more hydrophilic polymers, one or more hydrophobic polymers and/or one or more hydrophobic materials, the Timmins composition must contain at least one hydrophilic polymer, as shown by reference to all of the enabling examples of that patent and by the requirement of Timmins that the dosage form must swell. The Examiner has pointed to col.8, lines 29-45 of Timmins where it was pointed out that the extended release material is formed of one or more hydrophilic polymers and/or one or more hydrophobic polymers and/or one or more hydrophobic materials. This part of Timmins must be read in context with col. 20, lines 59-61 where Timmins described that the tablet of his invention "would swell up to three times its dry size" after ingestion.

If one argues that the Timmins recitation of "and/or" in connection with "hydrophilic polymers", "hydrophobic polymers" and "hydrophobic materials, teaches the individual use of each of these three materials, to the exclusion of the other materials, then an explanation must be given as to how the Timmins tablet would swell three times its size if it had no hydrophilic polymer. Amended claim 1 points out that the micro matrix particles consist of an active drug and a hydrophobic agent. This language excludes the hydrophilic agent.

Therefore, in the implementation of the teachings of Timmins, a skilled person in the art would be directed to use at

least one hydrophilic polymer in following the teachings of Timmins as to the making a sustained release formulation. Claim 1 of the present application points out a formulation where the micro matrix particles consist of hydrophobic polymers and a particular high dose, high solubility active ingredient. Claim 1, the claims that are dependent on claim 1 and claim 75 point out that the dosage form consists of the recited ingredients which do not include a hydrophilic component as required by Timmins. Hence, Timmins does not make the instant invention obvious. Claim 1 specifically recites micromatrix particles that use only hydrophobic polymers to prepare the sustained release component.

Furthermore, it is not disputed that matrix formulations of highly soluble drugs will require high amounts of polymers to achieve a controlled release profile. This results in an increase in the size of the dosage form and has been acknowledged by Timmins. The knowledge of the increased size does not suggest the dual retard technique as pointed out in claim 1 and the claims that depend from claim 1, in the present application. Thus, Timmins does not teach how one can reduce the overall size of dosage form while incorporating high amounts of drug in the composition.

In the Office Action, the Examiner pointed out that Timmins discloses a control release delivery system that includes (1) an inner solid particulate phase.., and (2) an outer solid continuous phase in which the granules of inner solid particulate phase are embedded and dispersed throughout. This means that Timmins discloses a biphasic formulation in which matrix formulation is used in both phases, inner and outer phase. Whereas the present invention uses a new technique called dual retard technique, which is a combination of a matrix formulations and a reservoir formulation, instead of matrix formulations in both phases as taught by Timmins. In this dual retard technique, first

the micromatrix particles of the high solubility dose active ingredient and one or more hydrophobic release controlling agents are formed (matrix formulations) and then these are further coated (reservoir formulations) with one or more release controlling agents (micromatrix particles are not dispersed or embedded as in Timminis). This dual retard release technique significantly reduces the amount of release controlling agents which are otherwise required in very high quantity and make the dosage form very bulky and therefore pose difficulty in swallowing. The other advantages of present invention is that it reduces the chances of dose dumping, unnecessary burst effect and failure of the system, which are otherwise usually associated with simple matrix or reservoir system.

The applicant has amended claim 1, added a phrase wherein said inner and said outer portions control the release of said high dose high solubility active ingredient by functioning as a dual retard release system. The dual retard technique is a combination of a matrix formulation and a reservoir formulation that provides a dual retard system.

The specification at paragraph [0098], discloses that: "FIGS. 6 and 7 show release of high dose, high solubility active agent 11 & 12 and 15 & 16 as per example 1 & 2 respectively from a dosage form prepared using dual retard technique as described in the present invention and the release of high dose, high solubility active agent 13 & 14 and 17 & 18 as per example 3 & 4 respectively from a dosage form prepared without using dual retard release technique. The total quantity of the hydrophobic release controlling agent is the same in all the dosage forms in spite of the fact that the figures clearly show that dual retard technology significantly reduces the burst effect and effectively controls the release rate of the high dose, high solubility active

ingredient for prolonged period. Paragraph [0162] also discloses the same conclusion.

The Timmins dosage form does not have any of the advantages of the presently claimed invention.

Timmins discloses the general conditions in the description (on which examiner rely) like, a large range of drug 10-98% of the inner solid particulate phase (column 9, lines 59-61). The extended release material in the form of hydrophobic polymer and/or other hydrophobic material are in the range of about 5-95% by weight, based on the weight of the inner solid particulate phase (column 9, lines 62-67 of Timmins.

However the ranges Timmins disclosed/claimed a very broad ranges, almost the entire range for drug and polymer, whereas present invention claimed restricted weight ratio of drug and polymer in micromatrix particle to very narrow range from 100:2.5 to 100:30. The Timmins weight ratio for the inner solid particulate phase to the outer solid continuous phase is within a range of 0.5:1 to 4:1 (column 9, lines 54-58 of Timmins). The present invention, as pointed out in claim 1, provides a weight ratio of particles:coating of 100:2.5 to 100:30, which is comparatively very narrow.

The dosage range of meteformin 150-3000mg (column 20, lines 21-28 of Timmins) could result in a dosage form of about 6,000mg + added weight for an immediate release drug, which is not possible to swallow.

The Examiner has cited at page 10 of the Office Action certain pictures of tablets from Timmins. It is requested that the Examiner clarify which pictures are being referred to as the applicant is unaware of any pictures that are in the file of the present application.

Timmins never exemplified the use of hydrophobic material by itself and the complete range of polymers is not exemplified in

the examples. Hence, only general disclosure of entire range does not make obvious an invention that contradicts the Timmins concept of providing ingredients that swells three times (col. 20, line 60) its size to prevent the formulation from leaving the stomach for an extended period of time. In addition, the inventors have surprisingly found that the amount of polymers is significantly reduced as compared to the prior art and gives an unexpected advantage to reduce the tablet size and prevent the burst release by using dual retard technique. Thus, It is not only optimization of the workable ranges but practical and workable ranges along with novel and different technique (Dual retard) makes the present invention inventive over prior art. For these reasons, it is requested that this ground of rejection be withdrawn.

The present invention teaches the use of hydrophobic release controlling agents, which do not hinder the release of the immediate release active ingredients (column 2, paragraph 28 & 57). The combination of Timmins and Boswell does not make the claimed invention obvious. If one skilled in the art combines the teachings of Timminis with the teachings of Boswell, one obviously would try the same composition of Timminis and use hydrophilic polymers to provide sustained release by swelling mechanism, which Timmins teaches as the mechanism for the release of the immediate release active ingredients. The present invention uses hydrophobic polymers which do not hinder the release of immediate release active ingredients, but prevent a burst release or dose dumping and provide a means for making a smaller size of tablet.

The applicant wants to draw kind attention of learned examiner towards MPEP § 2145 (X) (D) REFERENCES TEACHES AWAY FROM THE INVENTION OR RENDER PRIOR ART UNSATISFACTORY FOR INTENDED PURPOSE & MPEP § 2141.02 (VI) PRIOR ART MUST BE CONSIDERED IN ITS ENTIRETY, INCLUDING DISCLOSURES THAT TEACHES AWAY FROM THE CLAIM (W.L. Gore & Associates Inc. v. Garlock, Inc., 721 F. 2d. 1540,

220 USPQ 303 (Fed. Cir. 1983)). The prior art (Timmins) also teaches away from the use of hydrophobic polymers as the description states (column 2, lines 42-47) that "Hydration of any polymer matrix used to formulate the dosage form is a pre-requirement of establishing a stable release rate. Thus, a readily hydrating polymer is required to establish the desired stable release rate. However, if the polymer used is slow to hydrate, then an undesirable variable burst can occur". It is known to a skilled person that hydration is possible only with the polymers which are hydrophilic in nature and polymers that are slow to hydrate are hydrophobic in nature. This statement in Timmins regarding the hydration of the polymer matrix coupled with Timmins unequivocal disclosure that the dosage form swells "three times", (col. 30, line 61) teach directly away from the use of a hydrophobic polymer. The use of a hydrophobic polymer is contrary to the swelling requirement of Timmins

The present invention uses a hydrophobic polymer to prevent a burst release. Timmins disclosure of the need for the dosage formulation to hydrate is actually a warning that the use of a hydrophobic polymer can produce an undesirable variable burst.

It is also noted by the applicant that Timmins discloses that in a controlled release dosage form, the formulator tries to reduce the rate of dissolution by, for example, embedding the drug in a polymer matrix or surrounding it with a polymeric barrier membrane through which drug must diffuse to be released for absorption. To reduce the rate of release of drug from the dosage form to an appropriate level consistent with the blood level profile desired for a drug possessing a very high water solubility, very large amounts of polymer would be required for the matrix or barrier membrane (column 2, lines 16-33).

The applicant would like to point out that Timmins discloses a technique for either embedding or surrounding a core with a polymeric membrane, where as the present invention used a dual retard technique which is a combination of matrix and reservoir formulations. This combination is not disclosed or made obvious by the prior art. Timmins also agreed with the use of high amounts of polymer, whereas the inventor of the present invention has not only simply merged both the technique, but found unexpected advantages of controlled release with reduced amount of polymer, acceptable size of tablet, to overcome the burst effect.

In Timmins, the final size of the dosage form becomes very large due to large quantity of hydrophilic polymer required and thus the Timmins approach to formulations of drugs that must be administered in high doses (e.g., 1000mg) such as metformin, is not practical due the difficulty the patient will have in swallowing a very large size dosage form. This problem is exacerbated in older patient populations who often take these medications.

The instant invention, as pointed out in claim 1, is directed to a combination containing a high dose of a highly soluble drug in a sustained release form and a low dose drug in immediate release form. Thus, if Timmins approach of formulation is adopted the final dosage form will become very large and unpalatable.

The following Table is derived from Timmins and it illustrates the high amounts of polymer relative to the active pharmaceutical ingredient (API) that result from the Timmins technique.

Example-1	500g API + 376.5g polymer	75% polymers by wt of API

Example-2	500g API + 391g polymer	78% polymers by wt of API
Example-3	500g API + 408 g polymer	81% polymers by wt of API
Example-4	500g API + >400 g polymer	81% polymers by wt of API

If we compare examples for the preparation of micromatrix particles of the same drug as shown in the present specification (e.g. Example 6 & 9 having about 26-28% polymer), the final size of the dosage form will actually be much smaller as compared to the Timmins dosage form. This will make it possible to combine a high dose, high solubility drug in sustained release form with low dose active in IR form and at the same time to restrict the size of the dosage form. This is clear from all the examples of the Timmins, which only contains 500mg of drugs, whereas with instant invention it has become possible to prepare dosage form of 1000mg of active that too in combination with other drug, while keeping the size of final dosage form suitable for swallowing.

Thus, it is clear from above that the problem, if the teachings of Timmins are applied, any person skilled in art would end up having large sized dosage form for highly soluble drugs.

Although it is noted that the Timmins has covered a range of metformin from 1 to 3 gms once daily, but the final tablet weight is of approximately 1gm for 500mg of drug, so one can assume a tablet weight of 6gms for 3gms of drug, which is unrealistic to consume by a patient. This is the precise reason, Timmins prior art has used 2 x 500 mg dosage for its bioequivalence study (example-5) because 1000mg dosage, if prepared according to technique of Timmins, would result in unpalatable dosage form (2gm). In comparison, the tablet weight of the present invention for 500mg of dose is about 643mg, so even

1000mg dosage is formulated it would not exceed total wt of around 1300mg, which would be comparably easy to swallow. Thus, inventors of this invention has kept this thing in mind and only provided dose which have some real significance (even for 1500mg of drug, the final weight of tablet goes up to 1929mg) which is much less than the final tablet weight of Timmins.

Timmins teaches a drug delivery system which achieves extended gastric residence by virtue of size but does degrade in vivo so as not to cause obstruction of the gastrointestinal tract. Thus, Timmins is strictly limited to gastroretentive dosage forms and teaches away from any other type of dosage form that does not swell in the stomach in order to retard its passage in the gastrointestinal tract.

Timmins does not teach such a specific combination of agents having different solubility. In addition, Timmins does not disclose or suggest a dosage form where the top surface is not covered by the outer portion as pointed out in claims 1 and 75.

Boswell discloses medicinal tablets, and in particular, a tablet of the type containing substantially segregated quantities of the same or different ingredients. Boswell discloses a tablet having two different ingredients particularly when they are incompatible and which needs to be protected or separated from one another.

Boswell also discloses that either the inlay portion or the main body portion must be formed from a coated granulation to resist assimilation in the gastrointestinal fluids (col. 3 lines 30-35) by having an enteric coated component. It further describes a tablet having a main body portion and two separate inlay portions at opposite sides of the tablet. In applying the teachings of Boswell, any skilled person would be motivated to formulate the inlay tablet having at least an enteric coated

component in order to resist assimilation of one of the active ingredient in the gastrointestinal fluids.

None of the prior art teaches such a technique for high dose high solubility drugs, which reduces burst effect and also reduces the size of the dosage form.

The following chart compares a dosage from made by the assignee of the Timmins patent and a dosage form according to the present invention,. This comparison shows the reduction in size that is possible by the present invention.

Comparison of Commercial Tablet (US appl. No. 10/630,446 vs. BMS-Assignee of cited prior art i.e. Timmins)

Product detail	Product content	Shape	Weight of the product	Dimensions(length x width x thickness)
Glucophage XR as per prior art ; Timmins	Metformin sustained release (500mg)	Capsule shaped	1020.0mg	19.11mm x 9.4mmx 6.7 mm
Product of US application no: 10/630,446 (Enselin2 MF)	Rosiglitazone 2mg+ Metformin Sustained Release 500mg Tablet	Capsule shaped	784.0mg containing inner/outer portion weighing 90.0mg/694.0mgrespectively	14.95mm X 8.35mm x 6.3mm

For these reasons, Timmins alone or in combination with Boswell does not teach the claimed dosage form which uses a reduced quantity of polymers to control the release of a high dose, high soluble drug while providing a compact dosage form suitable for swallowing.

The applicant would like to point out that MPEP § 716.02 (a) I & IV GREATER THAN EXPECTED RESULTS ARE EVIDENCE OF

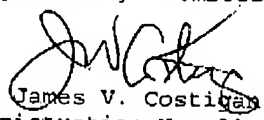
NONOBVIOUSNESS & ABSENSE OF AN EXPECTED PROPERTY IS EVIDENCE OF NONOBVIOUSNESS *Ex parte The NutraSweet Co.*, 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991).The unexpected and surprising advantages of the claimed invention have been pointed out above. These results are unexpected because a skilled person can only expect from the teachings of Timmins and Boswell that by using a biphasic process, to obtain a burst release, hindered release of immediate release active agent because of the using a hydrophilic polymer which would require a tablet having an unacceptable size which is difficult to swallow. It is surprisingly that the use of reduced amount of polymer (only hydrophobic) by the dual retard technique allows for the making of a tablet having an acceptable size, no burst release and no hindered release of an immediate release active agent. These results are of real significance and have practical advantages. These results were not expected by the teaching of Timminis and Boswell. So it is requested to withdrawn all the grounds of rejections based on 35 USC § 103.

For these reasons, it is requested that this ground of rejection be withdrawn.

In response to the objection to claim 12, this claim has been amended to recite that the coating "consists of" the recited ingredients so that it does not expand on claim 1 from which it depends. The objection to claims 32, 55 and 72 has been rendered moot by the cancellation of those claims. Misnumbered claim 73 has been amended to point out that it is claim 75. Claim 1 has been amended to clarify what is the inner portion and the outer portion so that the micromatrix only refers to the outer portion. Markush language has been used as a transition phrase for the recitation of the specific low dose and high dose pharmaceuticals in claims 1 and also in claims 5, 15 and 75. For these reasons, it is requested that this ground of rejection be withdrawn.

An early and favorable action is earnestly solicited.

Respectfully submitted,



James V. Costigan
Registration No. 25,669

Hedman & Costigan, P.C.
1230 Avenue of the Americas 7th Floor
New York, NY 10020
(212) 302-8989